Section A -Research paper

FECAL MARKERS IN PARKINSON'S DISEASE: REVIEW

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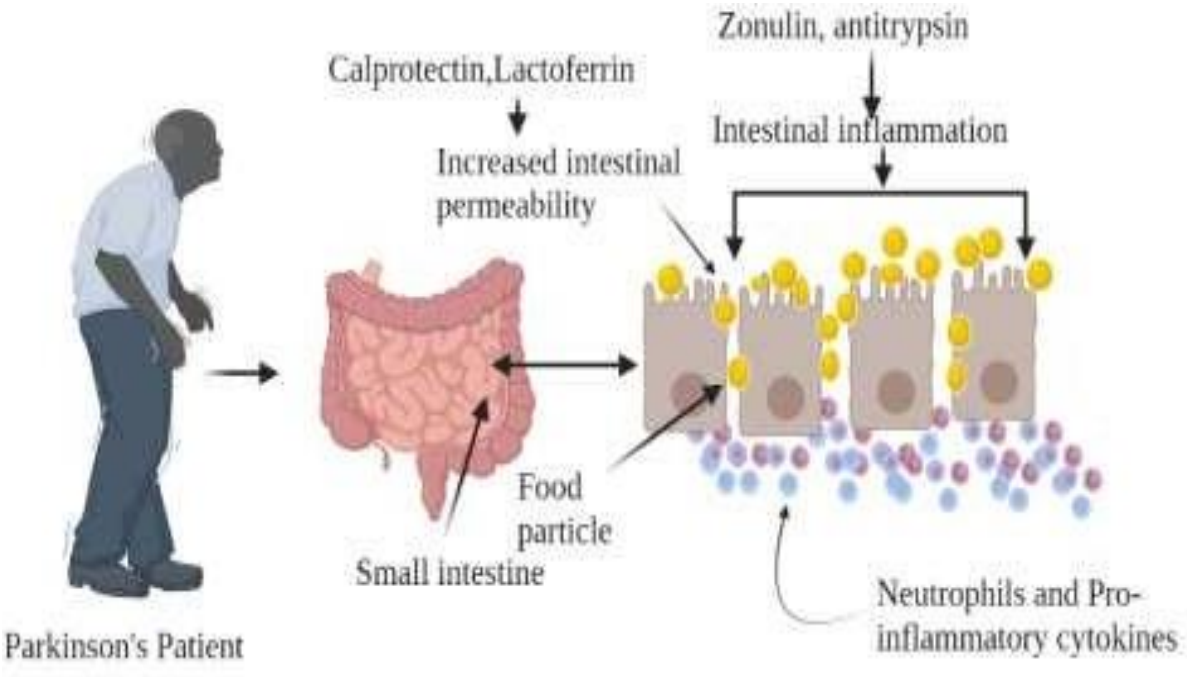
Abstract: In this present review, Fecal markers such as calprotectin, lactoferrin, zonulin and alpha-antitrypsin are found in stool samples and show elevated in Parkinson's Disease Patients. Fecal markers are the biologically active protein which is released in the stool either leaked from the gut or released by the intestinal mucosa. As per case studies cited in the review reveals that calprotectin and lactoferrin are responsible for Intestinal inflammation however, zonulin and alpha-antitrypsin are responsible for intestinal permeability in PD.

Graphical Abstract:



Keywords: Fecal Markers, Zonulin, Calprotectin, α-1-Antitrypsin, Lactoferrin

Introduction:

James Parkinson an English surgeon published 'Essay on the shaking palsy' in the Journal of neuropsychiatry classics in 1817 in his essay he first described Parkinson's Disease.[1] Parkinson's disease is a neurological disorder which pathologically characterized by loss of dopaminergic cells in the region Substantia niagra pars compacta (SNPC).[2,3] Nowadays diagnosis is on the basis of signs and symptoms. PD involves motor and non-motor symptoms, motors symptoms include bradykinesia, resting tremors, rigidity, postural instability and non-motor symptoms include such as insomnia, psychiatric disorders, depression, anxiety, apathy, impulse control disorder, dementia, cognitive impairment. Autonomic dysfunctions include drooling, orthostatic hypotension, gastrointestinal dysfunction, erectile dysfunction, excessive sweating, rapid eye movement, excessive daytime sleepiness and also other symptoms include pain, fatigue, olfactory functions, ophthalmic dysfunction.[4-6]

Multiple reasons for origin of PD. Genetic factors and environmental factors triggers the PD. higher risk is associated with above 50-60 year of age. In familial cases PD is caused by mutation in the alpha-synuclein gene, superoxide dismutase gene, glucocerebrosidase gene, leucine rich repeat kinase-2 gene, vacuolar protein kinase 2 gene, eukaryotic translation factor initiation factor 4 gamma 1 gene.[7] Several environmental toxins such as pesticides, herbicides, methanol, organic solvents, cyanides, carbon disulfides, which damages dopaminergic cells. other factors elevated cholesterol, head trauma, high calorie intake, increased body mass index, toxic metals, consumption of alcohol, cigarette smoking inflammation associated with activated microglia, methcathinone, mitochondrial dysfunctions, amphetamine abuse, generation of free radicals, nitric oxide toxicity, post-infection states and signal mediated apoptosis damages substantia niagra cells.[8-11]

Importance of Dopamine:

Dopamine is the one of important neurotransmitter in the central nervous system and it has functional network in the CNS. Pharmacologically dopamine receptors classified D1-D5 receptors and widely distributed in the brain.[12] D1 receptors located in the substantia niagra pars reticulata, nucleus accumbens, caudate putamen and kidneys D1 is functionally active for locomotion, memory attention, impulse control and regulation of renal function.[13,14] D2 receptors located in striatum, nucleus accumbens, hippocampus, amygdala, hypothalamus, cortex, heart, blood vessels, adrenal glands, sympathetic, ganglia, gastrointestinal tract and its functionally active for sleep, attention, memory, locomotion.[15-17] D3 receptors are located in substantia niagra, cortex, striatum, islands of Calleja and mast cells and it's functionally active for food intake, cognition, attention, locomotor and sleep.[18,19] D4 receptors are found in frontal cortex, amygdala, nucleus accumbens and functionally active for cognition, impulse control, hypothalamus, GI tract, kidneys, blood vessels, adrenal glands, sympathetic ganglia.[20,21] D5 receptors are found in cortex, olfactory tubercle hypothalamus, substantia niagra, heart, GI tract and its functionally active for cognition, attention, decision making, renal functions, GI motility.[22,23]

Gastric problems in Parkinson's disease:

As per research 50-60% Parkinson's Patients travelled through gastrointestinal problems such as constipation, bloating, gastroparesis, nausea, dysphagia, drooling, vomiting, leaky gut syndrome and intestinal inflammation.[24,25]

The connection between the gut and brain is interlinked with the vagus nerve and possesses a bidirectional pathway for understandings physiological signals. Alpha synuclein is a

neurological protein that abundantly available in synapse. The most popular and criticized Braack hypothesis state that alpha-synuclein accumulates in the gut and it's spread through the vagus nerve (X) in a prion-like manner.[26] The connection between the gut and brain is interlinked with the vagus nerve and possesses a bidirectional pathway for understandings the physiological signals.[27] Lewy bodies along with elevated mRNA expression of proinflammatory cytokines like TNF-alpha, Interleukins-1 beta, IL-6 and glial markers (Sox-10, S-100 beta, fibrillary acidic protein) play a vital role in gut inflammation.[27] In Parkinson's disease, intestinal inflammation and intestinal permeability are enhanced due to neuronal and peripheral oxidative stress, accumulation of alpha-synuclein in the brain and GIT track leads to loss of dopamine level in the brain.[28] Intestinal permeability is maintained by tight junction protein such as zona occludes. In PD intestinal inflammation is increased by oxidative stress hence it leads to increase intestinal permeability, which allows food particle enters into systemic circulation thus systemic inflammation is produced.[29]

Fecal markers in Parkinson's Disease:

Fecal markers provide specific indication of the disease condition and intestinal health and it's associated with gut immune system. These markers actively secreted by activation of gut immune system during the inflammation. As per clinical studies four fecal markers are secreted in PD, zonulin, antitrypsin, calprotectin and lactoferrin. These fecal markers are non-invasive, rapid, simple and low in cost. Its stable at -4 degree Celsius and quantitively measured by ELISA method.[30]

Table No:1 Cut off Values of Fecal Markers.

Sr.No.	Fecal Markers	Cut off value	Indication
1.	Calprotectin	50-51 µg/g	Intestinal permeability
2.	Lactoferrin	3 µg/g	Intestinal permeability
3.	Zonulin	78 ng/ml	Intestinal inflammation
4.	Antitrypsin	56 mg/dL	Intestinal inflammation

1. Calprotectin:

Calprotectin is a zinc-calcium binding protein which belongs to S-100 protein family which is occur in neutrophils in the human body. The other names for calprotectin are MRP8-MRP14, calgranulin A and B, cystic fibrosis antigen, L1, 60BB antigen, and 27E10 antigen The molecular weight of the calprotectin is 36kD. 60% calprotectin found in the cytosol of the neutrophil's plasma, urine, cerebrospinal fluid, feces.[30] It is least amounts present in the macrophages, monocyte and squamous epithelium. It's also found in the pus and abscess. The presence of calprotectin in the feces which indicate inflammation in the GI track. Presence of increased calprotectin doesn't contribute to the Parkinson's disease but it having role in the intestinal inflammation of PD. Elevated calprotectin not only present in the Parkinson's Disease but also present in the infectious gastroenteritis, acute appendicitis, peptic ulcer disease, cystic fibrosis, coeliac disease, transplant rejection and graft versus host disease. In the Parkinson's disease calprotectin is not disease specific but its contributing in the hypothesis of intestinal inflammation.[31]

Recent clinical studies shows that the higher level of fecal calprotectin was present in the stool of (36) Parkinson's Patients (14 females, 22 males) out of 36 patients, 17 patients (47.2%) show higher level fecal calprotectin. The study conducted at the Wroclaw Medical

University in Poland which were includes 35 Parkinson's Patients (19 males,16 females) in that 43% Parkinson's Patients indicate abnormal value of fecal calprotectin. The cut off value was the normal fecal calprotectin 51 µg/g for patients below 60 years of age, and 112 µg/g for patients above 60 years.[32]Increased calprotectin which induced bowel inflammation (17%) as well as other GI disturbances like constipation (69%), feeling of incomplete evacuation (51%), abdominal pain (21%), bloating (51%), and intestinal inflammation observed in the study.[31]

The positive indications of fecal calprotectin in the Parkinson's disease which activates gut immune system. calprotectin plays an important role in many physiological functions which includes promote pro-inflammation, growth differentiation, cell proliferation, apoptosis, motility, promote chemotaxis similarly cellular expression involves migration, adhesion and phagocytosis in neutrophils. Calprotectin is intestinal inflammatory markers which is indicate intestinal barrier dysfunction. The fecal calprotectin indicates the gut immune system activation, and its lucidly observe in the Parkinson's patients. it's may possess complex link between formation of amyloid formation and neuroinflammatory cascade serving as a prospective diagnosis and potential therapeutic target.[33]

2. Lactoferrin:

Lactoferrin or lactotransferrin is the cationic glycosylated iron binding protein, it is a multifunctional protein belongs to the transferrin family. Molecular weight of the lactoferrin is about 80 kDa. present inside the neutrophils, releasing number of secondary granules of human polymorphic neutrophils. It is widely present in the secretory cells such as milk, saliva, tears and nasal secretion.[34]

Fecal lactoferrin 25 % coherently present in the Parkinson's Patients as per clinical study. Fecal Lactoferrin is noninvasive which indicate red flag in the Parkinson's disease. The fecal lactoferrin stool test (normal range 0-7.24 µg/mL) is performed by quantitively one-way ANOVA. This is stable for two weeks in feces at room temperature and much more stable when sample stored at ≤-20°C. There is no fixed physiological role of the lactoferrin. Lactoferrin leads intestinal inflammation by activating gut immune system.[35]

In the stool samples of the PD patients 9 out of 36 patients shows positive fecal lactoferrin level. but this is not indicating for positive approach towards of pathogenesis of Parkinson's Disease. also, there is a correlation between pathogenesis of Parkinson's disease - mucosal inflammation. Increased level of fecal lactoferrin direct reflects the mucosal as well as intestinal inflammation. Lowers the WBC count and positive CRP values along with presence of Fecal lactoferrin which indicates the mucous intestinal inflammation in the neurodegenerative disorders. Fecal lactoferrin is not Parkinson's disease specific biomarkers but its contributing pathology of mucosal inflammation of many more disease. Like inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), colonic inflammation, Parkinson's Disease, Crohn's disease, ulcerative colitis and pathological conditions associated with gut brain axis.[36]

The major non motors symptoms of the Parkinson's disease are chronic constipation and GI irritability and colonic inflammation in rare cases. as per popular Braak hypothesis, alpha synuclein forms Lewy bodies and that s via Enteric nervous system through the vagus nerve to the central nervous system. These Lewy bodies produces colonic inflammation, IBD, IBS and leaky gut. Fecal lactoferrin is shows activation immune response and secretion of the Fecal Lactoferrin mount directly proportional to the neutrophils which migrates towards GI which promote the inflammatory mediators.[37]

3. Zonulin:

Human zonulin is called as preheptaglonin-2 zonulin is tight junction protein located in the digestive track. It modulates the permeability of tight junctions between cells of the wall of the digestive tract. Zonulin discovered by Dr. Fasano in year 2000 and his team at the university of Maryland school of medicine. Zonulin is a human blood serum protein which is synthesize in liver cells and reversibly it regulates intestinal permeability**.** zonulin binds to epidermal growth factor receptor and which is activated by protease-2 receptor this ligand receptor complex this signaling pathway leads to zona occludens protein. quantitative gene expression exposes overexpression of zonulin which leads to autoimmune disorder and neurodegenerative disorders associated with tight junction dysfunction.[38]

Zonulin can be used as disease biomarkers in the neurodegenerative, autoimmune and tumoral disease. In a recent study noted that in the Parkinson's disease gut dysbiosis occurs along with increased intestinal permeability. Schwiertz and colleagues conducted clinical study and observed that, Parkinson's disease patients (16 out of 36) than control subjects (4 out of 28) showed increased levels of zonulin in the feces. In the clinical study its observed that in early Parkinson's there is also increased in intestinal inflammation and intestinal permeability. Another clinical study published in year 2021 by Laura Dumitrescu and colleagues its overserved that in sporadic Parkinson's disease fecal overexpressed zonulin level were found higher in 8 out of 22 patients. (36.4%) and none of the control.[39]

The exact role of zonulin is related to intestinal permeability and mucosal barrier. Increased fecal zonulin damage mucosal barrier also it interferes with change in sugar level of Parkinson's disease. And this increased zonulin breaks the tight junctions between epithelial intestinal cells it called leaky gut syndrome. Food particles release in the blood stream and it contribute to inflammation in the body so there are neutrophils migrates towards the damage of mucosal layers, so this peripheral inflammation may lead autoimmune disorder.[40] These includes multiple sclerosis, rheumatoid arthritis, asthma, and inflammatory bowel disease, celiac disease, type 1 diabetes, and juvenile nonalcoholic fatty liver disease zonulin is not Parkinson's disease specific marker.[41]

4. α-1-Antitrypsin:

Alpha-1-antitrypsin which is glycoprotein of 394 ammino acids and molecular weight is 52kD. this is synthesized in pulmonary cells, hepatocytes and intestinal alveolar cells, neutrophils, cornea. AAT is released in the blood stream via Golgi apparatus. Direct function of this glycoprotein to protect lungs cells from factors which regulate inflammation in the lungs tissues by inhibiting cathepsin G, serine proteases, neutrophil elastase, and proteinase-3. However, AAT having indirect role in Parkinson's Disease.[42] Detection of AAT antitrypsin in the feces of Parkinson's patients reflects loss of intestinal lumen as well as mucosal barrier integrity. Schwiertz and colleagues conducted clinical study and observed that, Parkinson's disease patients (27 out of 36.75%) than control subjects (8 out of 28,28.6%) showed increased levels of alpha-1-antitrypsin (AAT) in the feces. The cut value was the 56mg/dL for fecal AAT.[43]

The AAT is not disease specific marker but may contribute intestinal permeability and inflammation in the Parkinson's Disease.[43] Normal function of AAT which protects the lungs cells from proinflammatory mediators but the mutation in the SERPINA1 which can lead to non-functional AAT and its polymerize and accumulate inside the endoplasmic reticulum and misfolded AAT accumulate in the lungs as wells as hepatic cells which develop the liver fibrosis, cirrhosis, prolonged inflammation, and extracellular matrix accumulation in liver and lungs. polymorphism or misfolded AAT can cause an imbalance of metal ion which could be aggregation of alpha synuclein in Parkinson's and Alzheimer's disease.[44-46]

Zonulin and alpha-1 antitrypsin there are the most vital biomarkers which regulate the intestinal permeability. presence these two proteins inside the fecal samples of the Parkinson's disease which is responsible down regulation of tight junction of intestine also increased the paracellular permeability.[47]Apart from that, in the children random stool collection of alpha-1-antitrypsin was found in patients who belongs to inflammatory bowel disease, chronic diarrhea, allergic gastroenteropathy, celiac disease, non-specific colitis, acute Gastrointestinal bleeding. alpha-1-antitrpsin is not any disease specific marker.[48]There is no clear evidence its contributing in the pathology of Parkinson's, gastrointestinal and inflammatory bowel diseases.[49,50]

Conclusion:

With the minimal information that is available that gives a peek of the Fecal markers found in the stool samples of Parkinson's patients that are related to intestinal permeability and inflammation from clinical research. Similar to how faecal zonulin and alpha-1-antitrypsin these proteins increase intestinal permeability which leads to leaky gut syndrome, autoimmune disorder, and abdominal cramps. Fecal calprotectin and lactoferrin increases intestinal mucosal inflammation in Parkinson's Disease and also activates gut immune system. Two clinical cases investigations demonstrated that the active presence of Calprotectin, Zonulin, lactoferrin, and -1-antitrypsin in faecal samples from PD patients.

Conflict of Interest:

Authors declares no conflict of Interest

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